Neuromuscular manifestations of diabetes mellitus and other endocrine disorders

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Diabetic neuropathies

Spectrum: symmetrical

- Diabetic sensorimotor polyneuropathy
- Diabetic autonomic neuropathy
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in diabetes mellitus

(Tracy JA, et al, 2008)

Diabetic neuropathies

Spectrum: asymmetrical

- Diabetic cranial neuropathy
- Diabetic mononeuropathies
- Diabetic reticuloplexus neuropathies (DRPN)

(Tracy JA, et al, 2008)

Diabetic neuropathies

Diabetic sensorimotor polyneuropathy (DPN)

- Most common diabetic neuropathy
- Typically presents as a slowly progressive sensory deficit in a length-dependent fashion
- Most cases are mild or asymptomatic and detected on clinical examination and electrophysiological study
- In more severe cases, it involves motor fibers as well and can produce footdrop

Diabetic neuropathies

Diabetic sensorimotor polyneuropathy (DPN)

- Strong correlation of length of exposure to hyperglycemia and degree of neuropathy

- Correlation of severity of DPN and other microvascular complications of diabetes (retinopathy, proteinuria and microalbuminuria as well as glycosylated hemoglobin)

Diabetic neuropathies

Diabetic sensorimotor polyneuropathy (DPN)

- Etiology of DPN seems to relate to microvascular damage from chronic hyperglycemia-mediated direct metabolic effect
- Good glycemic control can delay and probably prevent the development of DPN
- Control of blood sugar and prevention of DPN are the most important way of dealing with DPN

Diabetic neuropathies

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in DM

- There is suggestion that DM patients may be at increased risk to develop CIDP
- A definite association has not been established
- Clinical symptoms of patients with DM and CIDP were not different from idiopathic CIDP

Diabetic neuropathies

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in DM

- Nerve conduction study of DM + CIDP patients tended to show low amplitude of CMAP and SNAP indicating the presence of diabetic polyneuropathy as well

- Response to immunomodulatory therapy may not be as good as in idiopathic CIDP

Diabetic neuropathies

Diabetic cranial neuropathy

- Oculomotor nerve (CN III) is most commonly affected
- Others: abducens (CN VI) and facial nerves (CN VII)
- It is unclear if the overall incidence of facial nerve palsy is higher in diabetic patients

Diabetic cranial neuropathy

Diabetic oculomotor nerve palsy

- Typically presents with eye pain and paresis of the oculomotor-innervated extraocular muscles and ptosis.

- Pupil is spared in most cases since the mechanism is ischemic. If there is pupillary involvement,
  a compressive lesion e.g. an enlarging aneurysm
  must be ruled out

- Prognosis is good and full recovery generally occurs

Diabetic neuropathies

Diabetic mononeuropathies

- Median neuropathy at the wrist (carpal tunnel syndrome)
- Ulnar neuropathy at the elbow (cubital tunnel syndrome)
- Peroneal neuropathy at the fibular head

Diabetic neuropathies

Diabetic reticuloplexus neuropathies (DRPN)

- Diabetic thoracic radiculopathy
- Diabetic lumbosacral radiculoplexus neuropathy (DLRPN)
- Diabetic painless motor predominant neuropathy
- Diabetic cervical radiculoplexus neuropathy

Diabetic thoracic radiculopathy

- A rare but important complication of DM
- Typically presents with severe pain and dysesthesia along the trunk, chest or abdomen wall
- Often prompts extensive workups for underlying chest or abdominal pathology

Diabetic thoracic radiculopathy

- Can be symmetrical and can involve several dermatomes
- Can be associated with marked weight loss
- Prognosis is good with good recovery, usually within months to a year without any specific treatment

A 60-year-old man with type II DM

- Noted painless left-sided footdrop while walking. This required the use of an orthosis but improved significantly over the next 4 months

- 6 months after onset, his symptoms became bilateral and he developed subacute severe burning pain with allodynia in both thighs, weakness of both hip flexors and right-sided foot drop

A 60-year-old man with type II DM

- Then, he had some improvement of his pain but worsening of his weakness over 4 months
- At the time of evaluation, nearly one year after onset, he was using a walker
- Type II DM, diagnosed 3 years ago, taking insulin and rosiglitazone
- No retinopathy nor nephropathy
- 2 years earlier, he developed left-sided pain in a lower thoracic region

A 60-year-old man with type II DM

O/E

muscle	R	L
HF	3	4
HE	4	5
Quad	3	4
Hams	3	4
TA	2	2
Peroneus	2	4
TP	3	5
Toe E/F	1/3	2/4

upper limb muscles = N

lower limb reflexes = ↓,0

absent light touch,
pin prick,
temperature sen

reduced vibration sen
at toes

A 60-year-old man with type II DM

Investigation:

FBS = N (81mg/dL), HbA1c = ↑ (6.6)

CBC, ESR, electrolyte, ANA, protein electrophoresis, immunofixation, ANCA, RF, hepatitis screen, HIV serology = negative or normal

CSF: cell 1 L, protein 97 mg/dL, sugar 84 mg/dL, cytology - negative

A 60-year-old man with type II DM

NCS/EMG showed fibrillations and long duration polyphasic motor unit potentials with reduced recruitment in multiple lumbosacral dermatomes consistent with active and chronic lumbosacral plexopathies

Quantitative sensory testing (QST) showed abnormal cooling and heat pain detection threshold

MRI of lumbosacral plexus was normal

A 60-year-old man with type II DM

Right superficial peroneal nerve biopsy was performed

- Teased fiber preparation showed that most fiber were undergoing active axonal degeneration

- Semithin epoxy section (methylene blue) showed severe loss of myelinated fibers in a multifocal distribution

A 60-year-old man with type II DM

Diagnosis: diabetic lumbosacral reticuloplexus neuropathy

Treatment: 12-week course of weekly intravenous methylprednisolone infusion (1 gm/dose).

Progress: He had marked improvement of pain and weakness

(Tracy JA, et al, 2009)

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN)

- Median age of presentation is 65 years
- Usually presents with acute to subacute onset of severe thigh or leg pain (aching, burning, sharp stabbing and allodynia)
- Pain is followed by weakness and atrophy of leg muscles
- Pain and weakness begin unilaterally or focally but become widespread and bilateral over time

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN)

- Numbness and tingling are very common
- Half of the patients have autonomic symptom
- NCS/EMG findings are those of axonal degeneration

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN)

- Cerebrospinal fluid shows elevated protein with normal cell count
- Primary pathology process is ischemic injury from microvasculitis
- Treat with steroids, intravenous immunoglobulin or plasma exchange
- Recovery is substantial but incomplete with residual pain and leg weakness

Diabetic neuropathies

Diabetic reticuloplexus neuropathies (DRPN)

- Diabetic thoracic radiculopathy
- Diabetic lumbosacral radiculoplexus neuropathy (DLRPN)
- Diabetic painless motor predominant neuropathy: a variant of DLRPN?
- Diabetic cervical radiculoplexus neuropathy

Conclusion

- Spectrum of DM neuropathy is large
- There can be nerve damage from metabolic injury, compressive injury, ischemic injury and immune-mediated process
- Treatment is different among these pathogenesis ranging from life style modification, glucose control to immunosuppressive medication

Endocrine myopathy

- Glucocorticoid excess
- Adrenal insufficiency
- Hyperthyroidism
- Hypothyroidism
- Growth hormone excess
- Hypopituitarism
- Hyperparathyroidism
- Osteomalacia
- Hypoparathyroidism

Muscle disorders associated with thyroid diseases

Hyperthyroidism

Pathogenesis:

- Thyroid hormone increases basal metabolic rate, skeletal heat production, and mitochondrial oxygen, pyruvate and malate consumption

- Thyroid hormone increases glucose uptake and glycolytic activity, and stimulates glycogenolysis in skeletal muscle

- Thyroid hormone accelerates muscle-protein catabolism

Hyperthyroidism

Clinical presentation:

- 80% have neuromuscular complaints
- > 50% have marked muscle weakness
  - Hyperthyroid (thyrotoxic) myopathy
  - Thyrotoxic periodic paralysis
  - Myasthenia gravis
  - Grave ophthalmopathy

Hyperthyroidism

Thyrotoxic myopathy

- F:M = 3-4:1
- Mean age of onset = end of 5th decade

- Weakness and atrophy: more common in older patients, incidence and severity is related to the duration of illness

Hyperthyroidism

Thyrotoxic myopathy

- Weakness is primarily proximal and is usually out of proportion to the amount of muscle wasting but severe wasting may occur
- Myalgia, fatigue and exercise intolerance are common
- Breathlessness and respiratory muscle weakness can occur
- Bulbar muscle may be involved

Hyperthyroidism

Thyrotoxic periodic paralysis

- Much more prevalent in Asian people (2% of thyrotoxic patients in China VS 0.1% of those in USA)
- More prevalent in male than female (M:F = 10:1)
- Age 20 – 40 years
- Weakness can be limited to limb muscles or generalized, and lower limb muscles may be affected first

Hyperthyroidism

Thyrotoxic periodic paralysis

- Weakness may last from several hours to a few days
- Respiratory muscles may be involved in severe attacks
- Attacks may be triggered by carbohydrate loading or rest after exercise
- Hypokalemia is always present

Hypokalemia and paralysis in Thai population

A study of 34 Thai patients with periodic paralysis (PP) and hypokalemia:

- 11 (32%) = thyrotoxic PP, M > F
- 8 (24%) = distal renal tubular acidosis, F > M
- 15 (44%) = hypokalemic PP, M > F

  2/3 = sporadic, 1/3 = familial

(Phadeekitcharoen B, et al., 2004)

Thyrotoxic periodic paralysis

- Of the 11 patients with thyrotoxic PP, 8 (82%) had no previous history of thyroid disease

- Four out of 11 (36%) had only subtle signs of hyperthyroidism

Thyrotoxic periodic paralysis

Treatment

- IV potassium infusion (at slow rate,
  10 mEq/hr to avoid rebound hyperkalemia)
- Beta-adrenergic blocker (propranolol) may be beneficial in patients who do not respond to IV potassium
- Treat hyperthyroidism
- Avoid high carbohydrate meal and strenuous exercise
- Avoid glucocorticoids which can lower serum K^+

Hyperthyroidism

Myasthenia gravis (MG)

- MG patients have an increased incidence of thyroid disorders
- In general, 5 - 6% of MG patients are hyperthyroid. However, the incidence in Thai patients may be up to 17.5% (Ratanakorn D, et al, 2002)
- 2 -10% of MG patients are hypothyroid
- Less than 1% of hyperthyroid patients suffer from MG
- The treatment of MG is independent from that of hyperthyroidism

Muscle disorders associated with thyroid diseases

Hypothyroidism

Pathogenesis:

- Hypothyroidism reduces basal metabolic rate by reducing mitochondrial oxidation, muscle oxidative enzyme activity and glucose uptake
- Impaired glycogenolysis which may contribute to cramp and fatigability
- Both protein synthesis and degradation are reduced with net protein catabolism

Hypothyroidism

Clinical presentation:

- Hypothyroid myopathy
- Entrapment neuropathy
- Sensorimotor neuropathy
- Myasthenia gravis

Hypothyroidism

Hypothyroid myopathy

- Majority of hypothyroid patients have muscle stiffness, myalgia, fatigability, weakness and cramp
- Mild proximal weakness is detected in 1/3 to 1/2 of hypothyroid patients
- Severe weakness with muscle enlargement are rarely seen
- Slow relaxation of deep tendon reflexes

Muscle disorders caused by glucocorticoid abnormalities

Glucocorticoid excess

- Adrenal overproduction of cortisol
  - Adrenal hyperplasia or neoplasia
  - Adrenocorticotropic hormone (ACTH) overproduction by pituitary or other neuroendocrine tumors
- Administration of exogenous glucocorticoids or ACTH

Muscle disorders caused by glucocorticoid abnormalities

Glucocorticoid excess

Pathogenesis:

- Glucocorticoids alter muscle lipid, carbohydrate and protein metabolism
- The main effect of glucocorticoids is to induce muscle protein catabolism
- Glucocorticoids induce preferential type 2 fiber atrophy
- Increased muscle activity (e.g. physical therapy) may partially prevent glucocorticoid-induced myopathy

Steroid myopathy

- Incidence of steroid myopathy varies but can be up to 60%
- Dose and duration of steroid administration vary but high total cumulative dose increases the likelihood of developing myopathy
- In general, < 1 month duration is unlikely to develop significant myopathy and dose of 10 mg/d is rather safe
- Women are more likely to develop steroid myopathy with the same steroid dose

Steroid myopathy

- Weakness usually develop insidiously
- Primarily proximal with the legs more severely involved
- Myalgia occurs frequently
- Usually have stigmata of glucocorticoid excess (cushingoid appearance)
- Fluorinated steroids (triamcinolone, betamethasone and dexamethasone) are more likely to produce weakness
- Serum levels of muscle enzymes are usually normal

Steroid myopathy

- Acute myopathy developed in patients who had steroid treatment and received mechanical ventilation and neuromuscular blocking agents (critical illness myopathy)
- Several factors appear to contribute to the rapid onset of weakness and wasting:

  1) Immobility that may accelerate the onset of myopathy
  2) Neuromuscular blocking agents that may potentiate the action of steroid
  3) Concurrent sepsis

Steroid myopathy

Treatment

- Decrease steroid dosage
- Switch to a nonfluorinated agent
- Alternate-day treatment regimen should be instituted when possible
- Exercise therapy should be encouraged in patients receiving steroid
- Patients with myopathy should receive physical therapy

Muscle disorders of calcium and vitamin D metabolism

- Primary hyperparathyroidism
- Secondary hyperparathyroidism
- Osteomalacia
- Hypoparathyroidism
- Tetany

Primary hyperparathyroidism
Secondary hyperparathyroidism
Osteomalacia

Pathogenesis:

- Muscle disorder results from elevation in parathyroid hormone (PTH) (1° & 2° hyperparathyroidism) and impaired vitamin D activity (2° hyperparathyroidism and osteomalacia)
- PTH functions to maintain extracellular Ca^{2+} concentration
- Effects on skeletal muscle are through alteration of serum Ca^{2+} and direct effect on muscle metabolism
- PTH stimulates protein degradation in skeletal muscle

Primary hyperparathyroidism
Secondary hyperparathyroidism
Osteomalacia

Pathogenesis:

- Cholecalciferol (D_3) = a steroid derived from diet or ultraviolet radiation conversion of provitamin D in the skin

- D_3 is hydroxylated twice, first in the liver to form 25-OH-D_3 and then in the kidney to form $1,25(OH)_2D_3$, the active form of vitamin D

Primary hyperparathyroidism
Secondary hyperparathyroidism
Osteomalacia

Pathogenesis:

- The second hydroxylation is inhibited by renal disease or hypoparathyroidism
- Activated vitamin D stimulates Ca^{2+} absorption in the gut, bone resorption and renal reabsorption of phosphate
- Vitamin D deficiency in animals produces muscle wasting, impairs force generation and delays relaxation

Primary hyperparathyroidism
Secondary hyperparathyroidism
Osteomalacia

Pathogenesis:

- Myofibrillar ATPase activity is reduced
- Protein synthesis is decreased which may explain muscle wasting
- Skeletal muscle from uremic animals shows changes similar to those in vitamin-D-deficient animals
- Patients with muscle weakness associated with chronic renal failure improve with $1,25(OH)_2D_3$ administration, which emphasizes the importance of impaired vitamin D metabolism in uremic myopathy

Primary hyperparathyroidism

- Usually affects patients between the 3th and 5th decade, more common in women
- 1°manifestations are polyuria, constipation, nausea and renal stones
- Proximal muscle weakness, wasting, fatigability and cramps

Primary hyperparathyroidism

- Routine assay of serum Ca^{2+} (↑ Ca^{2+}, alkaline phosphatase, ↓ phosphate) enables hyperparathyroidism to be diagnosed at an asymptomatic stage

- R_x: Parathyroidectomy corrects symptoms and improves strength

Secondary hyperparathyroidism: Renal failure

- Patients with chronic renal failure frequently develop 2° hyperparathyroidism with myopathy similar to that seen in 1° hyperparathyroidism

- Lower limb weakness predominates but all limb are affected with time

Secondary hyperparathyroidism: Renal failure

- PTH excess, uremic toxin, vitamin D deficiency, etc. have been suggested as causes of myopathy
- Hypocalcemia is 2° to impaired vitamin D production
- R_x: Vitamin D replacement reduces the incidence of myopathy and renal transplant improves weakness

Osteomalacia

- Osteomalacia may be caused by dietary deficiency, malabsorption of vitamin D or abnormal vitamin D metabolism
- About 1/3 of patients with osteomalacia have complaints of weakness, myalgia or fatigue with proximal weakness

Osteomalacia

- Myopathy may precede bony change of osteomalacia
- Serum Ca^{2+}, phosphate, alkaline phosphatase are ↑
- PTH level may be normal or increased
- Serum level of vitamin is required to confirm the diagnosis
- R_x: Myopathy improves with vitamin D replacement but may take up to 6 months

Hypoparathyroidism

- Usually caused by surgical excision of the parathyroid glands or infarction
- Pseudohypoparathyroidism is characterized by signs of hypoparathyroidism in association with distinctive skeletal anomalies and intellectual impairmrnt
- PTH level is normal or elevated in pseudohypoparathyroidism which is caused by a defective cellular response to PTH

Hypoparathyroidism

- Hypomagnesemia occurs in both pseudo- and true hypoparathyroidism
- The most frequent muscle disorder is tetany
- Signs of chronic myopathy are occasionally found in pseudo and true hypoparathyroidism

Endocrine myopathy

- ✓ Glucocorticoid excess
- Adrenal insufficiency
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- ✓ Hyperparathyroidism
- ✓ Osteomalacia
- ✓ Hypoparathyroidism